IN THE SPECIFICATION

Please replace the paragraph beginning at page 69, line 4, with the following rewritten paragraph:

Process 3: After addition of 2-bromomethyl-1,4-difluorobenzene (12.3 ml, 95.5 mmol) to a suspension of sodium 4-chlorobenzenesulfinate (19.0 g, 95.5 mmol) in butanol (200 ml), the mixture was heated under reflux for 5 hours. The solid thus precipitated was collected by filtration and dissolved in methylene chloride. The resulting solution was washed with brine, dried over $MgSO_4$, and concentrated. The solid thus obtained was recrystallized from hexane, whereby the title compound (12.3 g, 43%) was obtained as colorless needle crystals. The filtrate was extracted with methylene chloride. ~~The extract was washed with water and brine, dried over $MgSO_4$, and concentrated. The solid thus obtained was washed with hexane, and dissolved in diethyl ether. After removal of an insoluble matter, the residue was concentrated. The solid was recrystallized from hexane, whereby the title compound (12.7 g, 44%) was obtained~~.

IR (ATR) ν: 3089, 2991, 2943, 1581, 1496, 1315, 1279, 1213, 1149, 1090, 1080, 1012, 958, 816, 779, 756, 729, 708, 646, 517, 469 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.36(2H,s), 6.91(1H, td, J=9.0, 4.4Hz), 6.99-7.06(1H,m), 7.11(1H,ddd,J=8.3,5.6,3.2Hz), 7.45(2H,d,J=8.8Hz), 7.62(2H,d,J=8.8Hz).

MS (m/z): 303 (M^++H).

Please replace the paragraph beginning at page 262, line 2, with the following rewritten paragraph:

Under an argon atmosphere, a hexane solution of n-butyl lithium (1.53M, 3.92 ml, 6 mmol) was added dropwise to a tetrahydrofuran (10 ml) solution of 2-bromopyridine (572 μl,

6 mmol) at -78°C and the mixture was stirred for 30 minutes. To the resulting brown solution, 2,5-difluorobenzaldehyde (655 µl, 6 mmol) was added dropwise and the temperature of the mixture was gradually raised to room temperature. Water was added to the reaction mixture, followed by extraction with ethyl acetate. After drying the solvent, the residue obtained by concentration under reduced pressure was purified by silica gel chromatography, whereby the title compound (120 mg, 9%) was obtained as a white solid.
^{1}H-NMR (400MHz, $CDCl_3$) δ: 5.45(1H,br), 6.08 (1H,s), 6.87-7.15(3H,m), 7.2-7.3(2H,m), 7.65(1H,m), 8.56(1H,m).
mp: 65-66 °C.

Please replace the paragraph beginning at page 266, line 5, with the following rewritten paragraph:

Under a nitrogen atmosphere, 60% oil sodium hydride (605 mg, 15.1 mmol) was added in portions to methanol (10 ml) under ice cooling. Twenty minutes later, a dimethylformamide (20 ml) solution of 2-bromo-3-hydroxypyridine (2.5 g, 14.4 mmol) was added to the resulting mixture. The reaction mixture was distilled under reduced pressure to remove methanol and to the residue was added methyl iodide (0.94 ml, 15.1 mmol). The mixture was stirred at room temperature for 3 hours.

Please replace the paragraph beginning at page 288, line 9, with the following rewritten paragraph:

The residue was dissolved in dimethylformamide (5 ml), followed by the addition of 4-chlorobenzenethiol (74 mg, 0.51 mmol) and potassium carbonate (281 mg, 2.04 mmol) under a nitrogen atmosphere. The mixture was stirred at 50°C for 1 hour. After cooling to

room temperature, diethyl ether (50 ml) was added, and the mixture was washed with water and brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (hexane:ethyl acetate=1:1), whereby a mixture containing ~~the title compound~~ 4-[(4-chlorophenyl)thio]-(2,5-diflurophenyl)]pyridine was obtained.

Please replace the paragraph beginning at page 295, line 15, with the following rewritten paragraph:

To a tetrahydrofuran (10 ml) solution of 2-bromothiazole (180 μg, 2 mmol) was added dropwise a hexane solution of n-butyl lithium (1.57M, 1.40 ml, 2.2 mmol) at -78°C. After stirring for 10 minutes, 2,5-difluorobenzaldehyde (238 μl, 2.2 mmol) was added and while stirring, the temperature of the mixture was gradually raised to 0°C. The reaction was then quenched by the addition of an aqueous solution of ammonium chloride, followed by the addition of ether. The ether layer was washed with water and brine, and then, dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane:ethyl acetate=1:1), whereby the title compound (358 mg, 79%) was obtained as an oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.77(1H, d, *J*=4.0Hz), 6.33(1H, d, *J*=4.0Hz), 6.95-7.10(2H,m), 7.24 (1H,m), 7.34(1H, d, *J*=3.6Hz), 7.75(1H, d, *J*=3.6Hz).
IR (ATR) cm^{-1}: 3224, 1489, 1238, 1172, 1128, 818.
MS *m/z*: 228 (M^++H).

Please replace the paragraph beginning at page 571, line 17, with the following rewritten paragraph:

Under nitrogen atmosphere, a solution of the 2,5-dichloro-4-[(4-chlorophenylthio)-(2,5-difluorophenyl)methyl]pyridine (100 mg, 0.24 mmol) obtained in Example 342 and ~~4-morpholine ethylamine~~ 4-(2-aminoethyl)morpholine (200 μl) in 1,4-dioxane (1.0 ml) was stirred at 100°C for 2 days. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (40 ml). The solution was washed with water and brine, dried and then concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (3% methanol/chloroform), whereby the title compound (12 mg, 10%) was obtained as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.42 (4H, m), 2.54 (2H, d, J=6.0 Hz), 3.27 (2H, q, J=6.0 Hz), 3.67 (4H, m), 5.12 (br, 1H), 5.90 (1H, s), 6.61 (1H, s), 6.86-7.0 (2H, m), 7.06 (1H, m), 7.15 (2H, d, J=8.4 Hz), 7.16 (2H, d, J=8.4 Hz), 7.95 (1H, s).
MS m/z: 510 (M^++H).

Please replace the paragraph beginning at page 577, line 9, with the following rewritten paragraph:

Under nitrogen atmosphere, diisopropyl azodicarboxylate (~~128 l~~ 128 μl, 0.653 mmol) was added to a solution of the 2-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]-5-(hydroxymethyl)pyridine (178 mg, 0.435 mmol) obtained in Example 331, di-tert-butyl iminodicarboxylate (142 mg, 0.653 mmol) and triphenylphosphine (171 mg, 0.653 mmol) in tetrahydrofuran (5 ml) and the resulting mixture was stirred at room temperature for 5 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was then washed successively with water and brine. The organic layer thus obtained was dried over sodium sulfate and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography on a silica gel column. A fraction obtained from the elution portion with hexane:ethyl acetate = 4:1 was concentrated

under reduced pressure, whereby the title compound (78 mg, 0.128 mmol, 32%) was obtained as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.48 (18H, s), 4.78 (2H, s), 5.94 (1H, s), 6.93 (1H, td, J = 9.0, 4.4 Hz), 6.98-7.04 (1H, m), 7.38 (2H, d, J = 8.6 Hz), 7.56 (2H, d, J = 8.6 Hz), 7.58 (1H, d, J = 8.1 Hz), 7.71 (1H, dd, J = 8.1, 2.4 Hz), 7.96-8.00 (1H, m), 8.57 (1H, d, J = 2.4 Hz).

IR (ATR) cm^{-1}: 2979, 1795, 1727, 1695, 1492, 1392, 1367, 1328, 1255, 1224, 1132, 1087, 1033.

MS m/z: 609 (M^++H).

Please replace the paragraph beginning at page 579, line 23, with the following rewritten paragraph:

Under ice cooling, N-methylmorpholine (~~26 l~~ 26 μl, 0.234 mmol) and acetyl chloride (~~16 l~~ 16μl, 0.234 mmol) were added to a solution of the [6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]pyridin-3-yl]methylamine (40 mg, 0.0978 mmol), which had been obtained in Example 351, in dichloromethane (3 ml). The resulting mixture was stirred at room temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed successively with water and brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column. A fraction obtained from the elution portion with hexane:ethyl acetate = 2:3 was concentrated under reduced pressure, whereby the title compound A (low polarity compound) (15 mg, 0.0304 mmol, 40%) was obtained as a white powder and the title compound B (high polarity compound) (12 mg, 0.0266 mmol, 27%) was obtained as a white powder.

Compound A

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.43 (6H, s), 4.96 (2H, s), 5.93 (1H, s), 6.91 (1H, m), 6.98-7.03 (1H, m), 7.39 (2H, d, J = 8.5 Hz), 7.54-7.61 (2H, m), 7.55 (2H, d, J = 8.5 Hz), 8.02 (1H, m), 8.51 (1H, d, J = 1.7 Hz).

IR (ATR) cm^{-1}: 1712, 1689, 1573, 1492, 1423, 1369, 1319, 1267, 1201, 1149, 1079, 1029.

mp: 60-64°C.

MS m/z: 493 (M^++H).

Compound B

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.03 and 2.04 (3H, rotamers), 4.42-4.50 (2H, m), 5.89 (1H, brs), 5.93 (1H, s), 6.92 (1H, td, J = 9.1, 4.4 Hz), 6.97-7.02 (1H, m), 7.41 (2H, d, J = 8.1 Hz), 7.57 (2H, d, J = 8.1 Hz), 7.61 (1H, d, J = 8.1 Hz), 7.71 (1H, d, J = 8.1 Hz), 7.98-8.03 (1H, m), 8.54 (1H, s).

IR (ATR) cm^{-1}: 1650, 1673, 1525, 1486, 1430, 1396, 1355, 1319, 1280, 1230, 1147, 1085, 1016.

mp: 177-178°C.

MS m/z: 451 (M^++H).

Please replace the paragraph beginning at page 581, line 17, with the following rewritten paragraph:

To a solution of the 6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]pyridin-3-yl]methylamine hydrochloride (60 mg, 0.135 mmol) in dichloromethane (5 ml) were added N-methylmorpholine (~~180 l~~ 180 μl, 1.62 mmol), 4-dimethylaminopyridine (10 mg, 0.0819 mmol) and N,N-dimethylsulfamoyl chloride (~~66 l~~ 66μl, 0.609 mmol). The resulting mixture was stirred at room temperature for 24 hours. Water was added to the reaction mixture, followed by extraction with dichloromethane. The organic layer was washed successively

with a saturated aqueous solution of sodium bicarbonate and brine. The resulting organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography on a silica gel column. A fraction obtained from the elution portion with hexane:ethyl acetate = 3:2 was concentrated under reduced pressure, whereby the title compound (48 mg, 0.0930 mmol, 70%) was obtained as a white powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.76 (6H, s), 4.29 (2H, d, J = 6.4 Hz), 4.43 (1H, t, J = 6.4 Hz), 5.94 (1H, s), 6.92 (1H, m), 6.98-7.04 (1H, m), 7.41 (2H, d, J = 8.6 Hz), 7.58 (2H, d, J = 8.6 Hz), 7.66 (1H, d, J = 8.1 Hz), 7.79 (1H, dd, J = 8.1, 2.5 Hz), 8.02 (1H, m), 8.61 (1H, d, J = 2.5 Hz).

mp: 177-178°C.

MS m/z: 516 (M^++H).

Please replace the paragraph beginning at page 582, line 24, with the following rewritten paragraph:

Under ice cooling, N-methylmorpholine (~~10 l~~ 10μl, 0.0881 mmol) and ethyl chloroglyoxylate (~~9 l~~ 9μl, 0.0807 mmol) were added to the 6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]pyridin-3-yl]methylamine (30 mg, 0.0734 mmol), which had been obtained in Example 351, in dichloromethane (4 ml). The resulting mixture was stirred at room temperature for 1 hour. Water was added to the reaction mixture, followed by extraction with dichloromethane. The organic layer was then washed successively with a saturated aqueous solution of sodium bicarbonate and brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography on a silica gel column. A fraction obtained from the elution portion with

hexane:ethyl acetate = 3:2 was concentrated under reduced pressure, whereby the title compound (28 mg, 0.0550 mmol, 76%) was obtained as a white powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.39 (3H, t, J = 7.1 Hz), 4.37 (2H, q, J = 7.1 Hz), 4.55 (2H, d, J = 5.9 Hz), 5.94 (1H, s), 6.89-6.94 (1H, m), 6.98-7.05 (1H, m), 7.40 (2H, d, J = 8.3 Hz), 7.56 (2H, d, J = 8.3 Hz), 7.53 (1H, brs), 7.62 (1H, d, J = 8.1 Hz), 7.72 (1H, d, J = 8.1 Hz), 7.97-8.03 (1H, m), 8.58 (1H, s).

mp: 193-194°C.
MS m/z: 509 (M^++H).

Please replace the paragraph beginning at page 584, line 3, with the following rewritten paragraph:

Triethylamine (~~45 l~~ 45μl, 0.324 mmol), 4-dimethylaminopyridine (5 mg, 0.0449 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (21 mg, 0.108 mmol) and N-p-tosylglycine (25 mg, 0.108 mmol) were added to a solution of the 6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]pyridin-3-yl]methylamine hydrochloride (40 mg, 0.0898 mmol), which had been obtained in Example 354, in dichloromethane (6 ml). The resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with dichloromethane, followed by successive washing with water, a saturated aqueous solution of sodium bicarbonate and brine. The organic layer thus obtained was dried over magnesium sulfate and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography on a silica gel column. A fraction obtained from the elution portion with hexane:ethyl acetate = 2.3 was concentrated under reduced pressure, whereby the title compound (41 mg, 0.0661 mmol, 73%) was obtained as a white powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.44 (3H, s), 3.59 (2H, d, J = 6.4 Hz), 4.44 (2H, dd, J = 6.1, 2.8 Hz), 5.42 (1H, t, J = 6.1 Hz), 5.95 (1H, s), 6.91 (1H, m), 6.96-7.03 (2H, m), 7.33 (2H, d, J

= 8.3 Hz), 7.41 (2H, d, J = 8.6 Hz), 7.57 (2H, d, J = 8.6 Hz), 7.58 (1H, d, J = 8.1 Hz), 7.66 (1H, dd, J = 8.1, 2.4 Hz), 7.74 (2H, d, J = 8.3 Hz), 8.01 (1H, m), 8.49 (1H, d, J = 2.4 Hz).

mp: 217-218°C.

MS m/z: 620 (M^++H).

Please replace the paragraph beginning at page 585, line 17, with the following rewritten paragraph:

Triethylamine (~~12 l~~ 12μl, 0.0881 mmol), 4-dimethylaminopyridine (5 mg, 0.0367 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (17 mg, 0.0881 mmol) and N,N-dimethylglycine (9 mg, 0.0881 mmol) were added to a solution of the 6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]pyridin-3-yl]methylamine (30 mg, 0.0734 mmol), which had been obtained in Example 351, in dichloromethane (5 ml). The resulting mixture was stirred at room temperature for 14 hours. The reaction mixture was diluted with dichloromethane, followed by successive washing with water, a saturated aqueous solution of sodium bicarbonate and brine. The organic layer thus obtained was dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column. A fraction obtained from the elution portion with hexane:ethyl acetate = 1:4 was concentrated under reduced pressure, whereby the title compound (21 mg, 0.0425 mmol, 58 %) was obtained as a white powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.30 (6H, s), 3.01 (2H, s), 4.50 (2H, d, J = 6.1 Hz), 5.93 (1H, s), 6.91 (1H, m), 6.98-7.04 (1H, m), 7.40 (2H, d, J = 8.6 Hz), 7.55 (2H, d, J = 8.6 Hz), 7.60 (1H, d, J = 8.1 Hz), 7.62 (1H, brs), 7.69 (1H, dd, J = 8.1, 2.4 Hz), 8.02 (1H, m), 8.56 (1H, d, J = 2.4 Hz).

mp: 177-179°C.

MS m/z: 494 (M^++H).

Please replace the paragraph beginning at page 586, line 25, with the following rewritten paragraph:

Triethylamine (~~21~~ 21μl, 0.147 mmol), 4-dimethylaminopyridine (7 mg, 0.0610 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (28 mg, 0.147 mmol) and N-formyl-4-(methylamino)benzoic acid (26 mg, 0.147 mmol) were added to a solution of the 6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]pyridin-3-yl]methylamine (50 mg, 0.122 mmol), which had been obtained in Example 351, in dichloromethane (5 ml). The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with dichloromethane, followed by successive washing with water, a saturated aqueous solution of sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography on a silica gel column. A fraction obtained from the elution portion with hexane:ethyl acetate = 3:7 was concentrated under reduced pressure, whereby the title compound (60 mg, 0.105 mmol, 87%) was obtained as a colorless amorphous substance.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.35 (3H, s), 4.67-4.71 (2H, m), 5.94 (1H, s), 6.53 (1H, brs), 6.90 (1H, m), 6.97-7.03 (1H, m), 7.25 (2H, d, J = 8.6 Hz), 7.40 (2H, d, J = 8.6 Hz), 7.56 (2H, d, J = 8.6 Hz), 7.63 (1H, d, J = 8.1 Hz), 7.78 (1H, dd, J = 8.1, 2.2 Hz), 7.86 (2H, d, J = 8.6 Hz), 8.03 (1H, m), 8.61 (1H, s), 8.64 (1H, d, J = 2.2 Hz).
MS m/z: 570 (M^++H).

Please replace the paragraph beginning at page 599, line 21, with the following rewritten paragraph:

Pyridine (0.040 ml, 0.49 mmol) and methylchloroformate (0.019 ml, 0.24 mmol) were successively added to a solution of the 2-[(4-chlorophenylsulfonyl)(2,5-

difluorophenyl)methyl]-5-(hydroxymethyl)pyridine (50 mg, 0.12 mmol), which had been obtained in Example 331, in dichloromethane (2 ml) at 0°C and the resulting mixture was stirred at room temperature for 1 hour. Methyl chloroformate (0.019 ml, 0.24 mmol) was then added to the reaction mixture at 0°C, followed by stirring at room temperature for 5 hours. The reaction mixture was washed with 1N hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography. A fraction obtained from the elution portion with hexane:ethyl acetate = 4:1 was concentrated under reduced pressure. The solid thus obtained was washed with hexane and collected by filtration, whereby the title compound (50 mg, 0.11 mmol, 88%) was obtained as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.81 (3H, s), 5.18 (2H, s), 5.95 (1H, s), 6.89-7.04 (2H, m), 7.40 (2H, d, J = 8.5 Hz), 7.55 (2H, d, J = 8.5 Hz), 7.65 (1H, d, J = 8.1 Hz), 7.78 (1H, dd, J = 8.1, 2.2 Hz), 7.97-8.03 (1H, m), 8.64 (1H, d, J = 2.2 Hz).

MS m/z: 468 (M^++H).

Please replace the paragraph beginning at page 601, line 13, with the following rewritten paragraph:

To a solution of the[6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]pyridin-3-yl]carbaldehyde (100 mg, 0.25 mmol), which had been obtained in Example 335, in dichloromethane (3 ml) were added N-methylmorpholine (~~32 l~~ 32μl, 0.29 mmol) and hydroxylamine hydrochloride (26 mg, 0.36 mmol). The resulting mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with dichloromethane, followed by successive washing with water, a saturated aqueous solution of sodium bicarbonate and brine. The organic layer thus obtained was dried over magnesium sulfate and concentrated under

reduced pressure. The residue was subjected to flash chromatography on a silica gel column. A fraction obtained from the elution portion with hexane:ethyl acetate = 3:2 was concentrated under reduced pressure, whereby the title isomer 373-A (low polarity compound) (79 mg, 0.19 mmol, 72%) was obtained as a white powder and the title isomer 373-B (high polarity compound) (17 mg, 0.040 mmol, 17%) was obtained as a white powder.

Isomer 373-A

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.97 (1H, s), 6.91-6.96 (1H, m), 6.99-7.05 (1H, m), 7.40 (2H, d, J = 8.6 Hz), 7.56 (2H, d, J = 8.6 Hz), 7.66 (1H, d, J = 8.1 Hz), 7.78 (1H, s), 7.96-8.02 (2H, m), 8.14 (1H, s), 8.75 (1H, d, J = 1.7 Hz).

IR (ATR) cm^{-1}: 3237, 1589, 1594, 1475, 1428, 1394, 1322, 1280, 1236, 1151, 1083, 1014.

mp: 187-188°C.

MS m/z: 423 (M^++H).

Isomer 373-B

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.98 (1H, s), 6.91-6.97 (1H, m), 7.00-7.06 (1H, m), 7.40 (1H, s), 7.41 (2H, d, J = 8.6 Hz), 7.57 (2H, d, J = 8.6 Hz), 7.71 (1H, d, J = 8.3 Hz), 7.90-8.02 (2H, m), 8.41 (1H, dd, J = 8.3, 2.1 Hz), 9.00 (1H, s).

IR (ATR) cm^{-1}: 3037, 1569, 1492, 1430, 1394, 1324, 1276, 1236, 1153, 1081, 1012.

mp: 194-196°C.

MS m/z: 423 (M^++H).

Please replace the paragraph beginning at page 602, line 31, with the following rewritten paragraph:

Triethylamine (~~32 l~~ 32μl, 0.23 mmol), 4-dimethylaminopyridine (12 mg, 0.095 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (44 mg, 0.23 mmol) and aminomethylcyclohexane (~~30 l~~ 30μl, 0.23 mmol) were added to a solution of the [6-[(4-

chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]pyridin-3-yl]carboxylic acid (80 mg, 0.19 mmol), which had been obtained in Example 338, in dichloromethane (5 ml). The resulting mixture was stirred at room temperature for 4.5 hours. The reaction mixture was diluted with dichloromethane, followed by successive washing with water, a saturated aqueous solution of sodium bicarbonate and brine. The organic layer thus obtained was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column and a fraction obtained from the elution portion with hexane:ethyl acetate = 3:1 was concentrated under reduced pressure, whereby the title compound (58 mg, 0.11 mmol, 59%) was obtained as a white powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.95-1.80 (11H, m), 3.32 (2H, d, J = 6.4 Hz), 5.98 (1H, s), 6.13-6.16 (1H, m), 6.90-6.96 (1H, m), ~~7.00-706~~ 7.00-7.06 (1H, m), 7.40 (2H, d, J = 8.6 Hz), 7.55 (2H, d, J = 8.6 Hz), 7.69 (1H, d, J = 8.3 Hz), 7.97-8.02 (1H, m), 8.13 (1H, dd, J = 8.3, 2.2 Hz), 8.94 (1H, d, J = 2.2 Hz).

MS m/z: 519 (M^++H).

Please replace the paragraph beginning at page 604, line 14, with the following rewritten paragraph:

Triethylamine (~~32 l~~ 32μl, 0.23 mmol), 4-dimethylaminopyridine (12 mg, 0.095 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (44 mg, 0.23 mmol) and 2-amino-5-chloropyridine (29 mg, 0.23 mmol) were added to the [6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]pyridin-3-yl]carboxylic acid (80 mg, 0.19 mmol), which had been obtained in Example 338, in dichloromethane (5 ml). The resulting mixture was stirred at room temperature for 5 hours. The reaction mixture was diluted with dichloromethane, followed by successive washing with water, a saturated aqueous solution of sodium bicarbonate and brine. The organic layer thus obtained was dried over magnesium

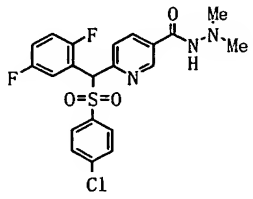
sulfate and then concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column and a fraction obtained from the elution portion with hexane:ethyl acetate = 3:1 was concentrated under reduced pressure, whereby the title compound (27 mg, 0.051 mmol, 27%) was obtained as a white powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.04 (1H, s), 6.92-6.97 (1H, m), ~~7.01-707~~ 7.01-7.07 (1H, m), 7.42 (2H, d, J = 8.6 Hz), 7.57 (2H, d, J = 8.6 Hz), 7.75 (1H, dd, J = 9.1, 2.4 Hz), 7.80 (1H, d, J = 8.1 Hz), 7.97-8.01 (1H, m), 8.26 (1H, dd, J = 8.1, 2.2 Hz), 8.28 (1H, d, J = 2.4 Hz) 8.33 (1H, d, J = 9.1 Hz), 8.51 (1H, s), 9.12 (1H, d, J = 2.2 Hz).

MS m/z: 534 (M^++H).

Please replace the heading and following paragraph beginning at page 605, line 9, with the following rewritten heading and paragraph:

Example 376: ~~N',N'-Dimethyl-6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]nicotinic acid hydrazide~~ 6-[(4-Chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]nicotinic acid N',N'-dimethyl hydrazide

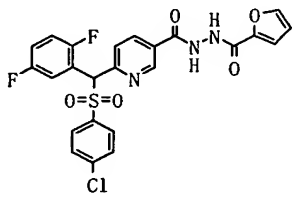


Triethylamine (~~32 l~~ 32μl, 0.23 mmol), 4-dimethylaminopyridine (12 mg, 0.095 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (44 mg, 0.23 mmol) and 1,1-dimethylhydrazine (~~21 l~~ 21μl, 0.23 mmol) were added to the [6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]pyridin-3-yl]carboxylic acid (80 mg, 0.19 mmol), which had been obtained in Example 338, in dichloromethane (5 ml). The resulting

mixture was stirred at room temperature for 7 hours. The reaction mixture was diluted with dichloromethane, followed by successive washing with water, a saturated aqueous solution of sodium bicarbonate and brine. The organic layer thus obtained was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column and a fraction obtained from the elution portion with dichloromethane:methanol = 50:1 was concentrated under reduced pressure, whereby the title compound (60 mg, 0.13 mmol, 68%) was obtained as a colorless amorphous substance.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.57 (0.9H, s), 2.72 (5.1H, s), 5.98 (1H, s), 6.48 (0.15H, s), 6.90-7.06 (2.85H, m), 7.41 (2H, d, J = 8.6 Hz), 7.56 (2H, d, J = 8.6 Hz), 7.68 (1H, d, J = 8.1 Hz), 7.97-8.04 (1H, m), 8.13-8.17 (1H, m), 8.94 (0.85H, s), 9.07 (0.15H, s).
MS m/z: 466 (M^++H).

Please replace the heading and following paragraph beginning at page 606, line 17, with the following rewritten heading and paragraph:

Example 377: ~~N'-(Furan-2-carbonyl)-6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]nicotinic acid hydrazide~~ 6-[(4-Chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]nicotinic acid N'-(furan-2-carbonyl) hydrazide



Triethylamine (~~32 l~~ 32μl, 0.23 mmol), 4-dimethylaminopyridine (12 mg, 0.095 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (44 mg, 0.23 mmol) and ~~2-furoic acid hydrazide~~ 2-furancarboxylic acid hydrazide (29 mg, 0.23 mmol) were added to a solution of the [6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]pyridin-3-

yl]carboxylic acid (80 mg, 0.19 mmol), which had been obtained in Example 338, in dichloromethane (5 ml). The resulting mixture was stirred at room temperature for 7.5 hours. The reaction mixture was diluted with dichloromethane, followed by successive washing with water, a saturated aqueous solution of sodium bicarbonate and brine. The organic layer thus obtained was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column and a fraction obtained from the elution portion with dichloromethane:methanol = 50:1 was concentrated under reduced pressure. The solid thus obtained was recrystallized from dichloromethane-hexane, whereby the title compound (58 mg, 0.11 mmol, 58%) was obtained as a white powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.01 (0.7H, s), 6.02 (0.3H, s), 6.55 (0.7H, dd, J = 3.4, 1.7 Hz), 6.91-6.96 (1H, m), 6.99-7.04 (1H, m), 7.21 (0.7H, d, J = 3.4 Hz), 7.41 (2H, d, J = 8.6 Hz), 7.53 (0.3H, dd, J = 1.7, 0.7 Hz), 7.56-7.60 (3H, m), 7.74 (1H, d, J = 8.3 Hz), 7.77 (0.3H, d, J = 8.8 Hz), 7.95-7.99 (1H, m), 8.15-8.19 (1H, m), 8.99 (0.3H, s), 9.03 (1H, d, J = 2.2 Hz), 9.14 (0.7H, brs), 9.67 (0.7H, brs), 9.98 (0.3H, brs).

MS m/z: 532 (M^++H).

Please replace the paragraph beginning at page 621, line 10, with the following rewritten paragraph:

Thionyl chloride (1.00 ml) and N,N-dimethylformamide (one drop) were added to a suspension of the [6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]pyridin-3-yl]carboxylic acid (100 mg, 0.236 mmol), which had been obtained in Example 338, in dichloromethane (4 ml). The resulting mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated to dryness. The residue was then dissolved in

dichloromethane (6 ml), followed by the addition of N-methylmorpholine (~~51.8 l~~ 51.8μl,, 0.472 mmol) and 4-methylcyclohexylamine (~~37.4 l~~ 37.4μl, 0.283 mmol). After the reaction mixture was stirred at room temperature for 18 hours, the mixture was diluted with dichloromethane. The solution was washed successively with 1N hydrochloric acid, water and brine, dried over magnesium sulfate and concentrated. The residue was subjected to flash chromatography on a silica gel column. A fraction obtained from the elution portion with hexane:ethyl acetate = 3:1 was concentrated, whereby a white solid was obtained. The resulting solid was recrystallized from ethyl acetate-hexane, whereby the title compound (70.3 mg, 0.135 mmol, 57%) was obtained as a white powder.
^{1}H-NMR (400 MHz, $CDCl_3$) δ:0.92 (1.8H, d, J = 6.6 Hz), 0.96 (1.2H, d, J = 6.4 Hz), 1.05-1.30 (3H, m), 1.32-1.43 (0.6H, m), 1.55-1.83 (4.4H, m), 2.03-2.12 (1H, m), 3.86-3.97 (0.6H, m), 4.20-4.28 (0.4H, m), 5.88 (0.6H, d, J = 7.1Hz), 5.98 (1H, s), 6.18 (0.4H, d, J = 7.3 Hz), 6.90-6.96 (1H, m), 6.98-7.06 (1H, m), 7.41 (1.2H, d, J = 8.1 Hz), 7.41 (0.8H, d, J = 8.1 Hz), 7.56 (1.2H, d, J = 8.1 Hz), 7.57 (0.8H, d, J = 8.1 Hz), 7.67-7.72 (1H, m), 7.97-8.05 (1H, m), 8.10-8.18 (1H, m), 8.93 (0.6H, d, J = 2.2 Hz), 8.96 (0.4H, d, J = 2.2 Hz).
IR (ATR) cm^{-1}: 3381, 2935, 1643, 1595, 1525, 1489, 1394, 1317, 1281, 1234, 1171, 1147, 1078, 1016, 966, 897, 831, 823, 764, 729, 609, 548, 469, 413.
MS m/z: 519 (M^++H).

Please replace the paragraph beginning at page 623, line 2, with the following rewritten paragraph:

To a suspension of the [6-[(4-chlorophenylsulfonyl)(2,5-difluorophenyl)methyl]pyridin-3-yl]carboxylic acid (100 mg, 0.236 mmol), which had been obtained in Example 338, in dichloromethane (6 ml) were added N-methylmorpholine (~~77.7 l~~ 77.7 μl, 0.708 mmol), o-methylhydroxylamine hydrochloride (23.6 mg, 0.283 mmol), and 1-

ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (54.3 mg, 0.283 mmol). After stirring at room temperature for 1 hour, tetrahydrofuran (1 ml) was added to the mixture. The reaction mixture was stirred at room temperature for 18 hours. The mixture was then diluted with dichloromethane, and washed with water and brine. The organic layer thus obtained was dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column and a fraction obtained from the elution portion with hexane:ethyl acetate = 1:1 was concentrated, whereby a white solid was obtained. The solid was washed with ethyl acetate, whereby the title compound (55.1 mg, 0.122 mmol, 52%) was obtained as a white powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.90 (2.4H, s), 3.97 (0.6H, s), 5.97 (0.2H, s), 5.98 (0.8H, s), 6.90-7.07 (2H, m), 7.39-7.46 (2H, m), 7.54-7.59 (2H, m), 7.63 (0.2H, d, J = 8.3 Hz), 7.73 (0.8H, d, J = 8.1Hz), 7.94-8.00 (1H, m), 8.10-8.15 (1H, m), 8.76 (1H, br s), 8.92 (0.8H, d, J = 1.7 Hz), 9.01 (0.2H, d, J = 1.5 Hz).

MS m/z: 453 (M^++H).

Please replace the paragraph beginning at page 635, line 25, with the following rewritten paragraph:

A solution of the 2,5-dichloro-4-[(4-chlorophenylthio)-(2,5-difluorophenyl)methyl]pyridine (60 mg, 0.14 mmol) obtained in Example 342 and ~~tert-butyl (morpholin-2-yl)methylcarbamate~~ (morpholin-2-yl)methylcarbamate tert-butyl (200 mg) in 1,4-dioxane (1.0 ml) was stirred at 100°C for 2 days under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (50 ml). The solution was washed with water and brine, dried and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (hexane: ether = 5:1), whereby the title compound (45 mg, 52%) was obtained as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.46 (9H, s), 2.72 (1H, m), 3.00 (1H, m), 3.22 (1H, m), 3.44 (1H, m), 3.6-3.75 (2H, m), 3.9-4.1 (3H, m), 4.95 (1H, br), 5.99 and 6.00 (1H, s, rotamer), 6.96 and 6.97 (1H, s, rotamer), 6.9-7.1 (3H, m), 7.24 (4H, s), 8.11 (1H, s).

MS m/z: 596(M^++H).